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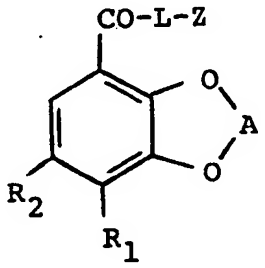

(I)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof wherein the variable groups are as defined in the specification.

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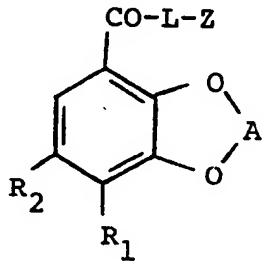
PHARMACEUTICALS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and their use as pharmaceuticals.

UK Patent No. 1571447 (Societe D'Etudes Scientifiques et Industrielles de L'Ile-de-France) describes a group of benzamide derivatives having dopamine antagonist activity.

A group of novel compounds have now been discovered, which compounds are 5-HT_3 receptor antagonists.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen, halo, nitro, amino, C_{1-6} alkyl or C_{1-6} alkoxy;

R_2 is halo, C_{1-6} alkyl or C_{1-6} alkoxy;

A is (poly)methylene of 1-3 carbon atoms, optionally substituted by one or two C_{1-6} alkyl group(s);

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain;

having 5-HT_3 receptor antagonist activity.

Suitable examples of alkyl moieties in R_1 and R_2 and A include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Suitable examples of halo moieties include fluoro, chloro and bromo, preferably chloro or bromo.

Often R_1 is hydrogen and R_2 is chloro or bromo.

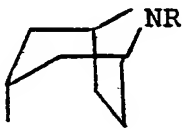
A is preferably unsubstituted polymethylene of 1 or 2 carbon atoms (i.e. O-A-O is methylenedioxy or ethylenedioxy).

Suitable examples of Z are described in the art relating to 5-HT_3 receptor antagonists, ie. as follows:

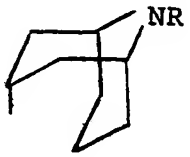
i) GB 2125398A (Sandoz Limited)
ii) GB 2152049A (Sandoz Limited)
iii) EP-A-215545 (Beecham Group p.l.c.)
iv) EP-A-214772 (Beecham Group p.l.c.)
v) EP-A-377967 (Beecham Group p.l.c.)
vi) PCT/GB91/01629 (Beecham Group p.l.c.)
vii) EP-A-358903 (Dianippon)

Particular side chains of interest are depicted thus:

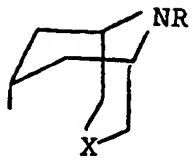
Tropane



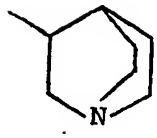
Granatane



Oxa/thia/aza-granatane



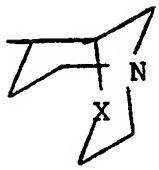
Quinuclidine



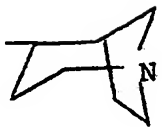
Isoquinuclidine

Isogranatane

Oxa/thia-isogranatane



Isotropane

 or 

wherein
R is hydrogen or methyl; and X is oxygen, sulphur or nitrogen optionally substituted by C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl, naphthyl, phenyl C_{1-4} alkyl or naphthyl C_{1-4} alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C_{1-6} alkoxy or C_{1-6} alkyl.

Side chains Z of particular interest include tropane, oxagranatane and azagranatane, where R is methyl. Suitable values for N-substituents when X is N are as described in PCT/GB91/01629, for example, iso-propyl or ethyl.

L is preferably NH.

Alternatively, COL in formula (I) may be replaced by a bioisostere therefor, for example, 1,2,4-oxadiazole and the other groups of structure h) described in EP-A-377967 (Beecham Group p.l.c.).

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

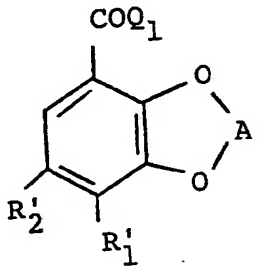
Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ′ (III)

or a reactive derivative thereof, when L is O;

wherein R_1', R_2' and/or Z′ are R_1, R_2 and/or Z respectively or groups or atoms convertible thereto; Q_1 is a leaving group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting R_1', R_2' and/or Z′ to another group or atom R_1, R_2, R_3 or Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-, activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-, or a nitrogen-linked heterocycle, such as imidazole.

If a group Q_1 is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or

dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0^{o}-100^{o}C, in particular 10-80^{o}C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene ordimethylformamide. It is also preferred that the group Q_1 is Cl_3CO- and that the reaction is carried out in toluene at reflux temperature.

When L is O the compound of formula (III) may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

It will be apparent that compounds of the formula (I) containing an R_1 or R_2 group which is convertible to another such group are useful novel intermediates. i.e. a hydrogen substituent is convertible to a halogen substituent by halogenation using conventional halogenating agents.

Z′ when other than Z may be wherein R is replaced by R′ which is a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo, C_{1-4} alkoxy and C_{1-4} alkyl. Such benzyl groups may, for example, be removed, when R_1/R_2 is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (I) wherein R is hydrogen.

This invention also provides a further process for the preparation of a compound of the formula (I) wherein R is

methyl or a pharmaceutically acceptable salt thereof, which comprises N-methylating a compound of formula (I) wherein R is hydrogen, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I). In this further process of the invention 'N-methylation' may be achieved by reaction with a compound CH_3Q_3 wherein Q_3 is a leaving group.

Suitable values for Q_3 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$, preferably Cl, Br or I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above.

Alternatively, 'N-methylation' may be effected under conventional reductive alkylation conditions.

Interconverting R in the compound of the formula (III) before coupling with the compound of the formula (II) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R/Z interconversion.

It is often convenient in the preparation of such a compound of formula (III) to prepare the corresponding compound wherein the methyl group is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding

compound of formula (II).

The compounds of formula (II) are known or are preparable analogously to, or routinely from, known compounds, such as described in UK 1571278.

Compounds of the formula (III) are generally prepared from the corresponding exocyclic keto derivative of the azabicyclic side chain, prepared by condensation methods, often using a substituted piperidine.

They may be prepared by processes described in the aforementioned Patent Publications relating to values of the side chain Z.

It will be realised that in the compounds of the formula (I) having a tropane, granatane or oxa/thia/aza-granatane side chain, the -COL- linkage has an **endo** orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of **endo** and **exo** isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the **endo** isomer may if desired by synthesised from the corresponding **endo** form of the compound of the formula (II). Corresponding geometric isomeric pairs are possible for the isoquinuclidine, isogranatane, oxa/thia-isogranatane and isotropane side chains.

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT_3 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis, includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT_3 receptor antagonists may also be of potential use in the treatment of obesity, arrhythmia, and/or disorders associated with myocardial instability.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional

excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such

as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a

compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders herein- before described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

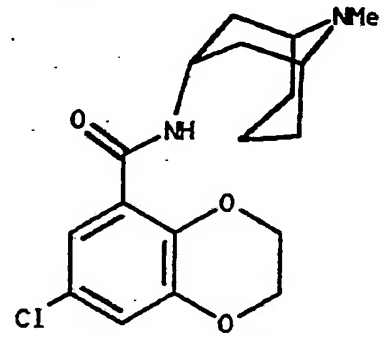
No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I).

Example 1

endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-7-chloro-1,4-benzodioxan-5-carboxamide (E1)



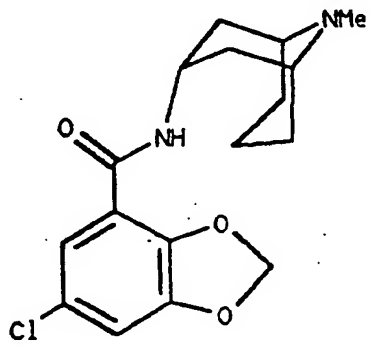
A solution of 7-chloro-1,4-benzodioxan-5-carboxylic acid (UK patent 1,571,278, Societe D'Etudes Scientifiques et Industrielles de L'Ile-de-France) (0.25g) in $SOCl_2$ (5 mL) was stirred at room temperature for 2h. The reaction mixture was evaporated to dryness and re-evaporated with xylene (2 x 20 mL). The residue was dissolved in CH_2Cl_2 (20 mL) and treated with a solution of **endo**-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (0.2g) in CH_2Cl_2 (10 mL). After standing at room temperature overnight, the reaction mixture was washed with sat. $NaHCO_3$ (50 mL), dried (K_2CO_3) and evaporated to dryness. The residue was purified by column chromatography (Al_2O_3, eluting with CH_2Cl_2) to give the title compound, converted to its HCl salt with ethanolic HCl, precipitation with Et_2O. (0.31 g).

^1H NMR (d^6-DMSO) δ 8.40, 8.20 (2-d, 1H)
7.10 (s, 2H)
4.65-4.15 (m, 5H including 4.30, brs, 4H)
3.65-3.45 (m, 2H)
2.81, 2.79 (2-s, 3H)
2.55-2.30 (m, 4H)
2.20-1.95 (m, 2H)
1.82-1.53 (m, 2H)
1.55-1.35 (m, 2H)

Prepared similarly was:

Example 2

endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-6-chloro-1,3-benzodioxole-4-carboxamide (E2)



^{1}H NMR ($CDCl_3$) δ7.51 (d, 1H)
6.88 (d, 1H)
6.72 (brd, 1H)
6.13 (s, 2H)
4.58-4.38 (m, 1H)
3.09 (brd, 2H)
2.60-2.40 (m, 5H including 2.50 s, 3H)
1.98 (brd 3H)
1.59-1.42 (m, 1H)
1.31 (dt, 2H)
1.03 (brd, 2H)

5-HT_3 Receptor Antagonist Activity

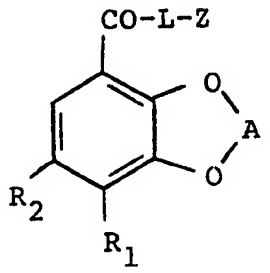
Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) is then determined.

The compounds of the Examples are both active at a dose of 10µg/kg i.v.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen, halo, nitro, amino, C_{1-6} alkyl or C_{1-6} alkoxy;

R_2 is halo, C_{1-6} alkyl or C_{1-6} alkoxy;

A is (poly)methylene of 1-3 carbon atoms, optionally substituted by one or two C_{1-6} alkyl group(s);

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain;

having 5-HT_3 receptor antagonist activity.

2. A compound according to claim 1 wherein R_1 is hydrogen and R_2 is chloro or bromo.

3. A compound according to claim 1 or 2 wherein O-A-O is methylenedioxy or ethylenedioxy.

4. A compound according to any one of claims 1 to 3 wherein the side chain Z is tropane, granatane, oxa/thia/aza-granatane, quinuclidine, isoquinuclidine, isogranatane, oxa/thia-isogranatane or isotropane.

5. A compound according to claim 4 wherein Z is tropane, oxagranatane or azagranatane.

6. A compound according to any one of claims 1 to 5 wherein L is NH.

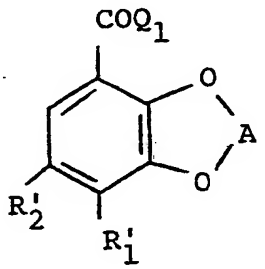
7. **endo**-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-7-chloro-1,4-benzodioxan-5-carboxamide.

8. **endo**-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-6-chloro-1,3-benzodioxole-4-carboxamide.

9. A pharmaceutically acceptable salt of a compound according to claim 7 or 8.

10. A compound according to claim 1 substantially as defined herein with reference to the Examples.

11. A process for the preparation of a comound according to claim 1, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ′ (III)

or a reactive derivative thereof, when L is O;

wherein R_1', R_2' and/or Z' are R_1, R_2 and/or Z respectively or groups or atoms convertible thereto; Q_1 is a leaving group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting R_1', R_2' and/or Z' to another group or atom R_1, R_2, R_3 or Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound according to claim 1.

14. A compound according to any one of claims 1 to 11 for use as an active therapeutic substance.

15. A compound according to any one of claims 1 to 11 for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

16. The use of a compound according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02173

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 451/00 C 07 D 451/04 C 07 D 451/06
C 07 D 451/14 C 07 D 453/02 C 07 D 453/06 C 07 D 487/08
C 07 D 498/08 A 61 K 31/395 A 61 K 31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 451/00 C 07 D 453/00 C 07 D 487/00 C 07 D 498/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0083737 (BEECHAM GROUP PLC) 20 July 1983, see abstract; claims 1,11-13; page 22, lines 12-22	1-4,6, 11,12, 14-16
X	CH,A, 651561 (DELALANDE S.A.) 30 September 1985, see abstract; claims 1,13	1-3,6
X	GB,A,1571447 (SOCIETE D§ETUDES SCIENTIFIQUES ET INDUSTRIELLES DE L'ILE-DE-FRANCE) 16 July 1980, see claims 1,15,17,92-95	1-6,12, 14-16
X	EP,A,0377967 (BEECHAM GROUP PLC) 18 July 1990, see claims 1,2,11,14,15,17	1,4-6, 11,12, 14-16

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° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17-02-1992	24. 03. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0041817 (BEECHAM GROUP LIMITED) 16 December 1981, see abstract; claims 1,8,13 ---	1-6,11, 12,14-16
X	EP,A,0226267 (BEECHAM GROUP PLC) 24 June 1987, see abstract; claims 1,5,6,9,13-15 -----	1-4,6, 11,12, 14-16

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 13 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv)
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif à la demande de brevet international n°

PCT/GB91/02173 SAE 54087

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

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